Table 8: **Protease**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Protease(3–11)	RT(71–79 clades A, B, D)	ITLWQRPLV		human(A*6802)	[Brander & Goulder(2001)]
	• C. Brander notes this is an A*6802 epitope				
Protease(3–11)	Protease(71–79 LAI)	ITLWQRPLV		human(A*6802, A*7401, A19)	[Dong(1998)]
	• Predicted on binding motif, no truncations analyzed • clade A/B/D consensus, S. Rowland-Jones, pers. comm.				
Protease(3–11)	RT(71–79 clades A, B, D)	ITLWQRPLV		human(A*7401)	[Brander & Goulder(2001)]
	• C. Brander notes this is an A*7401 epitope				
Protease(3–11)	Pol(59–65)	ITLWQRPLV	HIV-1 infection	human(A28)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
Protease(3–11)	RT(71–79 LAI)	ITLWQRPLV	HIV-1 infection	human(A28 supertype)	[Mollet (2000)]
	• Epitope name: P2. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses • In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished • Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change				
Protease(3–11)	Pol( )	ITLWQRPLV	HIV-1 exposed seronegative, HIV-1 infection	human(A74)	[Kaul (2001a)]
	• ITLWQRPLV cross-reacts with clades A, B and D • ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				
Protease(11–20)	Pol(91–100)	VTILIGGQLK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]
	• Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs				

- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Protease(12–20) Pol(92–100) TIKIGGQLK HIV-1 infection human(A3 supertype) [Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Protease(30–38) Pol( ) DTVLEEMNL HIV-1 exposed seronegative human(A*6802) [Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope: DTVLEDINL
- This epitope was recognized by two different exposed and uninfected prostitutes
- This epitope was identified by screening 49 HIV-1 peptides with the predicted A*6802 anchor residue motif x[VT]xxxxxx[VL]

Protease(30–38) pol( ) DTVLEDINL HIV-1 exposed seronegative human(A*6802) [Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

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Protease(30–38) RT(85–93 clade D) DTVLEEWNL human(A*6802) [Brander & Goulder(2001)]

- C. Brander notes this is an A*6802 epitope

Protease(30–38) Pol( ) DTVLEDINL HIV-1 infection human(A*6802) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- DTVLEDINL was recognized in 3 of the 6 women (ML857, ML1203, and ML1707), and the response was present in the last available sample prior to seroconversion, 3-7 months
- In each of the three women, 20/20 sequences of the infecting strain had no substitutions in this epitope, all were DTVLEDINL, so there was no evidence for escape

- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 3/22 HEPS sex worker controls, ML851, ML1432, and ML1601

Protease(30–38)	Pol(85–93)	DTVLEDINL	HIV-1 exposed seronegative, HIV-1 infection	human(A*6802)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A*6802 women, 11/12 HEPS and 6/11 HIV-1-infected women recognized this epitope likelihood ratio 4.4, p value 0.08, and HEPS women tended to respond to DTVLEDINL, infected women tended to respond to ETAYFYILKL
- The dominant response to this HLA allele was to this epitope in 10 of the 11/12 HEPS cases, but in only 4 of the 6/11 HIV-1-infected women
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILKD/EPVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLNM/TLNI/VV in p24 and B18 FRDYVDRFY/FK also in p24
- Subject ML 857 shifted from an A*6802 DTVLEDINL and B35 H/NPDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within the epitope
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A*6802 DTVLEDINL and A*6802 ETAYFILKL post-seroconversion

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Protease(45–54)	Pol(125–134)	KMIGGIGGFI	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus

- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

Protease(75–84) Protease(75–84 MN) VLVGPTPVNI *in vitro* stimulation human(A*0201) [Konya (1997)]

- Peptide predicted to be reactive based on HLA-A*0201 binding motif
- Peptide could stimulate CTL in PBMC from 5/6 seronegative donors
- Peptide located in a highly conserved region of protease
- Both 9-mer and 10-mer could stimulate CTL: VLVGPTPVNI and LVGPTPVNI
- Binding affinity to A*0201 was measured, $C\_1/2 \max \mu M = 6$ for 10-mer, 3 for 9-mer
- MAL variant of Pr(75-84 MN), with substitutions V77, G78, and P79, gave reduced binding and CTL recognition

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Protease(76–84) Pol( ) LVGPTPVNI HIV-1 infection human(A*0201) [Altfeld (2001d)]

- Epitope name: Pol-163. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- LVGPTPVNI binds to 4/5 HLA-A2 supertype alleles: A*0201, A*0202, A*0206 (highest affinity) and A*6802, but not A*0203
- 1/22 individuals with chronic HIV-1 infection recognized this epitope by ELISPOT
- 0/12 acutely infected individuals recognized this epitope

Protease(76–84) Pol(156–164) LVGPTPVNI HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)
